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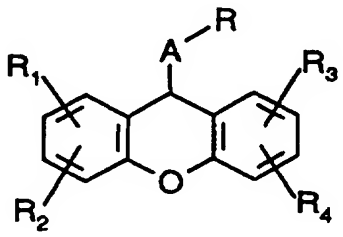
(54) Title: ANTI-NEURODEGENERATIVELY EFFECTIVE XANTHENE DERIVATIVES

(57) Abstract

Xanthene derivatives of formula (I) wherein A signifies methylene, carbonyl or thiocarbonyl, R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic radicals, and R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl, and their pharmaceutically employable salts, may be used as anti-neurodegenerative active ingredients for medicaments. The invention also relates to new compounds of formula (I).



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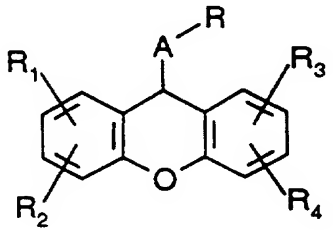
Anti-neurodegeneratively effective xanthene derivatives

The invention relates to the use of xanthene derivatives of formula I



(I),

wherein A signifies methylene, carbonyl or thiocarbonyl,
R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic or araliphatic radicals, and
R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,
and their pharmaceutically employable salts, as anti-neurodegenerative active ingredients for medicaments, or for the preparation thereof, as well as new compounds of formula I and their salts as such, processes for their production and pharmaceutical preparations containing them.

New compounds of formula I are for example those in which

a) at least one of radicals R_1, R_2, R_3 and R_4 is different from hydrogen, if R signifies amino, chloroacetylamino, 2-diethylaminoethylamino or piperidino, or if R represents lower-alkylamino, di-lower-alkylamino, pyrrolidino, morpholino or 4-lower-alkyl-piperazino and A represents carbonyl;

b) R_1 and R_3 are different from hydrogen, lower alkyl and halogen or R is different from optionally 4-lower-alkylated 4-amino- or 4-hydroxypiperidino, if R_2 and R_4 signify hydrogen and A is methylene;

c) R_1 is different from 2-methoxy, R_2 from 3-methoxy, R_3 from 7-methoxy or R_4 from 6-methoxy, if R is methylamino or acetylamino and A is methylene;

d) R_1 is different from 2-ethoxycarbonyl, R_3 from 7-chloro, if R is 4-methylpiperazino, R_2 and R_4 signify hydrogen and A represents methylene.

Amino groups mono- or di-substituted by monovalent aliphatic or araliphatic radicals are for example lower alkylamino; phenyl-lower-alkylamino or phenyl-lower-alkyl-lower-alkylamino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, di-lower-alkylamino-lower-alkinyl-lower-alkylamino, carboxy-lower-alkylamino, lower-alkoxycarbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, carboxy-lower-alkyl-lower-alkylamino, lower-alkoxycarbonyl-lower-alkyl-lower-alkylamino, carbamoyl-lower-alkyl-lower-alkylamino or cyano-lower-alkyl-lower-alkylamino.

Amino groups disubstituted by divalent aliphatic radicals are for example respectively 3- to 8-membered lower-alkylene-amino, lower-alkenyleneamino or lower-alkadienyleneamino; 3- or 4-aza-lower-alkyleneamino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkyleneamino or optionally S-oxidised 3- or 4-thia-lower-alkyleneamino, such as in particular pyrrolidino, pyrrolino (2,5-dihydropyrrol-1-yl), pyrrolo (pyrrol-1-yl), piperidino, di-lower-alkylpiperidino, tetrahydropyridino, such as 1,2,5,6-tetrahydropyridino or 1,2,3,4-tetrahydropyridino, dihydropyridino, such as 1,2-dihydropyridino, hexamethyleneimino, heptamethyleneimino, piperazino, N'-lower-alkylpiperazino, N'-hydroxy-lower-alkylpiperazino, N'-lower-alkoxy-lower-alkylpiperazino, N'-lower-alkanoylpiperazino, morpholino, thiomorpholino, S-oxothiomorpholino or S,S-dioxothiomorpholino.

Amino groups substituted by divalent araliphatic radicals are for example phenyl-lower-alkyleneamino or N'-phenyl-lower-alkylaza-loweralkyleneamino radicals either unsubstituted or substituted in the phenyl moiety by lower-alkyl, lower-alkoxy, halogen and/or trifluoromethyl.

In the preceding and following text, the lower radicals and compounds are understood to be for example those which have up to and including 7, preferably up to and including 4 carbon atoms (C-atoms).

Di(hydroxy-lower-alkyl)amino is for example N,N-di(hydroxy-C_2-C_4-alkyl)amino, such as N,N-di(2-hydroxyethyl)amino or N,N-di(3-hydroxypropyl)amino.

Di(lower-alkoxy-lower-alkenyl)amino is for example N,N-di(C_1-C_4-alkoxy-C_2-C_4-alkenyl)-amino, such as N,N-di(4-methoxy-but-2-enyl)amino.

Di(lower-alkoxy-lower-alkyl)amino is for example N,N-di(C_1-C_4-alkoxy-C_1-C_4-alkyl)amino, such as N,N-di(2-methoxyethyl)amino, N,N-di(2-ethoxyethyl)amino or N,N-di(3-methoxy-propyl)amino.

Di-lower-alkenylamino is for example N,N-di-C_2-C_4-alkenylamino, such as N,N-diallylamino or N-methallyl-N-allylamino.

Di-lower-alkylamino is for example N,N-di-C_1-C_4-alkylamino, such as dimethylamino, diethyl-amino, ethylmethylamino, dipropylamino, methylpropylamino, ethylpropylamino, dibutyl-amino or butylmethylamino.

Di-lower-alkylamino-lower-alkenyl-lower-alkylamino is for example N-(di-C_1-C_4-alkylamino-C_2-C_4-alkenyl)-N-C_1-C_4-alkylamino, such as N-(4-dimethylaminobut-2-enyl)-N-methylamino.

Di-lower-alkylamino-lower-alkenylamino is for example N-(di-C_1-C_4-alkylamino-C_2-C_4-alkenyl)amino, such as N-(4-dimethylaminobut-2-enyl)amino.

Di-lower-alkylamino-lower-alkinylamino is for example N-(di-C_1-C_4-alkylamino-C_2-C_4-alkinyl)-amino, such as N-(4-dimethylaminobut-2-inyl)amino.

Di-lower-alkylamino-lower-alkyl-lower-alkylamino is for example N-(di-C_1-C_4-alkylamino-C_2-C_4-alkyl)-N-C_1-C_4-alkylamino, such as N-(2-dimethylaminoethyl)-N-methylamino, N-(2-dimethylaminoethyl)-N-ethylamino, N-(3-dimethylaminopropyl)-N-methylamino or N-(4-dimethylaminobutyl)-N-methylamino.

Di-lower-alkylamino-lower-alkylamino is for example N-(di-C_1-C_4-alkylamino-C_2-C_4-alkyl)-amino, such as N-(2-dimethylaminoethyl)amino, N-(2-dimethylaminoethyl)amino, N-(3-dimethylaminopropyl)amino or N-(4-dimethylaminobutyl)amino.

Halogen is for example halogen with an atomic number of up to and including 35, such as chlorine or bromine.

Hydroxy-lower-alkenyl-lower-alkylamino is for example N-(hydroxy-C_2-C_4-alkenyl)-N-(C_1-C_4-alkylamino, such as N-(4-hydroxybut-2-enyl)-N-methylamino.

Hydroxy-lower-alkenylamino is for example hydroxy-C_2-C_4-alkenylamino, such as 4-hydroxy-but-2-enylamino.

Hydroxy-lower-alkinylamino is for example hydroxy-C_2-C_4-alkinylamino, such as 4-hydroxy-but-2-inylamino.

Hydroxy-lower-alkyl-lower-alkylamino is for example N-(hydroxy-C_2-C_4-alkyl)-N-C_1-C_4-alkyl-amino, such as N-(2-hydroxyethyl)-N-methylamino, N-(3-hydroxypropyl)-N-methylamino or N-(4-hydroxybutyl)-N-methylamino.

Hydroxy-lower-alkylamino is for example hydroxy-C_2-C_4-alkylamino, such as 2-hydroxyethyl-amino, 3-hydroxypropylamino or 4-hydroxybutylamino.

N'-hydroxy-lower-alkylpiperazino is for example N'-(hydroxy-C_1-C_4-alkyl)piperazino, such as N'-(2-hydroxyethyl)piperazino or N'-(3-hydroxypropyl)piperazino.

N'-lower-alkanoylpiperazino is for example N'-C_1-C_7-alkanoylpiperazino, such as N'-acetylpiperazino.

N'-lower-alkoxy-lower-alkylpiperazino is for example N'-(C_1-C_4-alkoxy-C_1-C_4-alkyl)piperazino, such as N'-(2-methoxyethyl)piperazino or N'-(3-methoxypropyl)piperazino.

N'-lower-alkylpiperazino is for example N'-C_1-C_4-alkylpiperazino, such as N'-methylpiperazino, N'-ethylpiperazino, N'-propylpiperazino or N'-butylpiperazino.

Lower alkoxy is for example C_1-C_7-alkoxy, preferably C_1-C_5-alkoxy, such as methoxy, ethoxy, propyloxy, isopropyloxy, butyloxy, isobutyloxy, secondary butyloxy, tertiary butyloxy, pentyloxy or a hexyloxy or heptyloxy group.

Lower-alkanoyloxy-lower-alkenyl-lower-alkylamino is for example N-(C_1-C_7-alkanoyloxy-C_2-C_4-alkenyl)-N-(C_1-C_4-alkyl)-amino, such as N-(4-acetoxybut-2-enyl)-N-methylamino.

Lower-alkanoyloxy-lower-alkenylamino is for example N-(C_1-C_7-alkanoyloxy-C_2-C_4-alkenyl)-amino, such as N-(4-acetoxybut-2-enyl)amino.

Lower-alkanoyloxy-lower-alkinyl-lower-alkylamino is for example N-(C_1-C_7-alkanoyloxy-C_2-C_4-alkinyl)-N-(C_1-C_4-alkyl)amino, such as N-(4-acetoxybut-2-inyl)-N-methylamino.

Lower-alkanoyloxy-lower-alkinylamino is for example N-(C_1-C_7-alkanoyloxy-C_2-C_4-alkinyl)-amino, such as N-(4-acetoxybut-2-inyl)amino.

Lower-alkanoyloxy-lower-alkyl-lower-alkylamino is for example N-(C_1-C_7-alkanoyloxy-C_2-C_4-alkyl)-N-(C_1-C_4-alkyl)amino, such as N-(2-acetoxyethyl)-N-methylamino, N-(2-acetoxyethyl)-N-ethylamino, N-(3-acetoxypropyl)-N-methylamino or N-(4-acetoxybutyl)-N-methylamino.

Lower-alkanoyloxy-lower-alkylamino is for example N-(C_1-C_7-alkanoyloxy-C_2-C_4-alkyl)amino, such as N-(2-acetoxyethyl)amino, N-(3-acetoxypropyl)amino or N-(4-acetoxybutyl)amino.

Lower-alkenyl-lower-alkylamino is for example N-(C_2-C_7-alkenyl)-N-(C_2-C_7-alkyl)-amino, especially N-(C_2-C_4-alkenyl)-N-(C_1-C_4-alkyl)-amino, such as N-vinyl-N-methylamino-N-allyl-N-methylamino, N-allyl-N-ethylamino, N-but-2-enyl-N-methylamino or N-but-3-enyl-N-methylamino.

Lower-alkenylamino is for example N-(C_2-C_7-alkenyl)amino, especially N-(C_2-C_4-alkenyl)-amino, such as vinylamino, allylamino, but-2-enylamino or N-but-3-enylamino, especially allylamino.

Lower-alkinyl-lower-alkylamino is for example N-(C_2-C_4-alkinyl)-N-(C_1-C_4-alkyl)-amino, such as N-propargyl-N-methylamino, N-but-2-inyl-N-methylamino or N-but-3-inyl-N-methylamino.

Lower-alkinylamino is for example N-(C_2-C_7-alkinyl)amino, especially N-(C_2-C_4-alkinyl)amino, such as propargylamino, but-2-inylamino or N-but-3-inylamino, especially propargylamino.

Lower-alkoxy is for example C_1-C_7-alkoxy, preferably C_1-C_4-alkoxy, such as methoxy, ethoxy, propyloxy, isopropyloxy or butyloxy, but may also be isobutyloxy, secondary butyloxy, tertiary butyloxy or a C_5-C_7-alkoxy group, such as a pentyloxy, hexyloxy or heptyloxy group.

Lower-alkoxy-lower-alkenyl-lower-alkylamino is for example N-(C_1-C_4-alkoxy-C_2-C_4-alkenyl)-N-N-(C_1-C_4-alkyl)-amino, such as N-(4-methoxybut-2-enyl)-N-(methylamino, N-(4-methoxybut-2-enyl)-N-ethylamino or N-(4-ethoxybut-2-enyl)-N-methylamino.

Lower-alkoxy-lower-alkenylamino is for example N-(C_1-C_4-alkoxy-C_2-C_4-alkenyl)amino, such as N-(4-methoxybut-2-enyl)amino or N-(4-ethoxybut-2-enyl)amino.

Lower-alkoxy-lower-alkinyl-lower-alkylamino is for example N-(C_1-C_4-alkoxy-C_2-C_4-alkinyl)-N-(C_1-C_4-alkyl)amino, such as N-(4-methoxybut-2-inyl)-N-methylamino, N-(4-methoxybut-2-inyl)-N-ethylamino or N-(4-ethoxybut-2-inyl)-N-methylamino.

Lower-alkoxy-lower-alkinylamino is for example N-(C_1-C_4-alkoxy-C_2-C_4-alkinyl)amino, such as N-(4-methoxybut-2-inyl)amino, N-(4-ethoxybut-2-inyl)amino or N-(4-propyloxybut-2-inyl)-amino.

Lower-alkoxy-lower-alkylamino is for example C_1-C_4-alkoxy-C_2-C_4-alkylamino, such as 2-methoxyethylamino, 2-ethoxyethylamino, 2-propyloxyethylamino, 3-methoxypropylamino, 3-ethoxypropylamino, 4-methoxybutylamino, 2-isopropyloxyethylamino or 2-butyloxyethylamino.

Lower-alkoxy-lower-alkyl-lower-alkylamino is for example N-(C_1-C_4-alkoxy-C_2-C_4-alkyl)-N-(C_1-C_4-alkyl)-amino, such as N-(2-methoxyethyl)-N-methylamino, N-(2-ethoxyethyl)-N-methylamino, N-(2-propyloxyethyl)-N-methylamino, N-(3-methoxypropyl)-N-methylamino, N-(3-ethoxypropyl)-N-methylamino or N-(4-methoxybutyl)-N-methylamino.

Lower alkyl is for example C_1-C_7-alkyl, preferably C_1-C_4-alkyl, such as methyl, ethyl, propyl, isopropyl or butyl, but it may also be isobutyl, secondary butyl, tertiary butyl or a C_5-C_7-alkyl group, such as a pentyl, hexyl or heptyl group.

Lower alkylamino is for example C_1-C_7-alkylamino, preferably C_1-C_4-alkylamino, such as methylamino, ethylamino, propylamino, isopropylamino or butylamino, but may also be isobutylamino, secondary butylamino, tertiary butylamino or a C_5-C_7-alkylamino group, such as a pentylamino, hexylamino or heptylamino group, and it is in particular methylamino or propylamino.

Lower-alkylamino-lower-alkylamino is for example N-(C_1-C_4-alkylamino,-C_2-C_4-alkyl)amino, such as N-(2-methylaminoethyl)amino, N-(1-methylaminoethyl)amino, N-(3-methylaminopropyl)amino, N-(4-methylaminobutyl)amino, N-(2-ethylaminoethyl)amino, N-(1-ethylaminoethyl)amino, N-(3-ethylaminopropyl)amino or N-(4-ethylaminobutyl)amino.

Lower-alkyleneamino-lower-alkylamino is for example 3- to 8-membered alkyleneamino-C_2-C_4-alkylamino, such as 2-pyrrolidinoethylamino, 2-piperidinoethylamino, 2-dimethylpiperidinoethylamino, 2-hexamethyleneiminoethylamino, 3-pyrrolidinopropylamino, 3-piperidinopropylamino, 3-dimethylpiperidinopropylamino or 3-hexamethyleneiminopropylamino.

Phenyl-lower-alkyl-lower-alkylamino is for example N-(phenyl-C_1-C_4-alkyl)-N-(C_1-C_4-alkyl)-amino, such as N-benzyl-N-methylamino, N-(2-phenylethyl)-N-methylamino or N-(4-phenylbutyl)-N-methylamino.

Phenyl-lower-alkylamino is for example phenyl-C_1-C_4-alkylamino, such as benzylamino, 1- or 2-phenylethylamino, 3-phenylpropylamino or 4-phenylbutylamino.

Phenyl-lower-alkyl-lower-alkyleneamino is for example phenyl-C_1-C_4-alkyl-pyrrolidino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, such as 2- or 3-benzylpyrrolidino; phenyl-C_1-C_4-alkylpiperidino such as 2-, 3- or 4-benzylpiperidino, furthermore phenyl-C_1-C_4-alkylhexahydroazepino such as 2-, 3- or 4-benzylhexahydroazepino, phenyl-C_1-C_4-alkylaziridino such as 2-benzylaziridino or phenyl-C_1-C_4-alkylazetidino such as 2- or 3-benzylazetidino.

N-phenyl-lower-alkylaza-lower-alkyleneamino is for example N'-phenyl-C_1-C_4-alkyl-imidazolidino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, such as N'-benzylimidazolidino, phenyl-C_1-C_4-alkylpiperazino such as N'-benzylpiperazino, or phenyl-C_1-C_4-alkylhexahydro-1,3-diazepino such as N'-benzylhexahydro-1,3-diazepino, furthermore phenyl-C_1-C_4-alkyl-1,3-diazetidino such as N'-benzyl-1,3-diazetidino, or phenyl-C_1-C_4-alkylpyridazino such as N'-benzylpyridazino.

Salts of compounds of formula I are for example the pharmaceutically employable acid addition salts thereof with appropriate mineral acids, such as hydrohalic acids, sulphuric acid or phosphoric acid, e.g. hydrochlorides, hydrobromides, sulphates, hydrogen sulphates or phosphates, or salts with appropriate aliphatic or aromatic sulphonic acids or N-substituted sulphaminic acids, e.g. methane sulphonates, benzene sulphonates, p-toluene sulphonates or N-cyclohexyl sulphaminates (cyclamates), similarly acid addition salts with pharmaceutically employable organic carboxylic acids, for example pharmaceutically employable acid addition salts with optionally hydroxylated lower alkanoic acids, e.g. acetic acid, propionic acid, pivalic acid, glycolic acid, pyroacemic acid, lactic acid or gluconic acid, optionally hydroxylated, aminated and/or oxo-substituted lower alkanedicarboxylic acids, e.g. oxalic acid, malonic acid, succinic acid, glutamic acid, aspartic acid, tartaric acid or malic acid, optionally hydroxylated and/or oxo-substituted lower-alkanetricarboxylic acids, e.g. citric acid or aconitic acid, optionally hydroxylated and/or oxo-

substituted lower-alkene-dicarboxylic acids, e.g. fumaric acid, maleic acid or itaconic acid, optionally hydroxylated and/or oxo-substituted lower-alkine-dicarboxylic acids, e.g. acetylene-dicarboxylic acid, furthermore with aromatic, hetero-aromatic or araliphatic carboxylic acids, such as benzoic acid, salicylic acid, phthalic acid, phenylacetic acid, mandelic acid, cinnamic acid or nicotinic acid.

The invention is based on the surprising discovery that compounds of formula I, when administered to newly-born rats in an experimental setup according to Ansari et al., J. Neuroscience 13, 4042-4053 (1993) at doses of approximately 0.1 mg/kg s.c. and less, have a marked protective effect of the facial motor neurones from apoptotic cytolysis, and when administered to fully-developed rats in an experimental setup according to Golowitz and Paterson, Soc. Neurosc. Abstr. 20, 246, 113.2 (1994) at 0.275 mg/kg s.c. and less over 4 days, have a marked protective effect of hippocampal pyramidal cells from cytolysis by administering kainic acid.

Similarly, compounds of formula I protect mesencephalic, dopaminergic neurones in culture at approximately 10-8 molar concentrations, from apoptotic cytolysis induced by MPP+.

Furthermore, it may be shown that when compounds of formula I are administered to mice at 0.14 mg/kg p.o. and less over 20 days, they effect a marked protective activity of thyrosin-hydroxylase-positive, nigral neurones from cytolysis by administering MPTP.

Accordingly, the compounds of formula I and their pharmaceutically employable salts are consequently eminently suitable for the prophylactic or therapeutic treatment of neurodegenerative disorders, especially those in which apoptotic cytolysis plays a role, such as cerebral ischaemia, Alzheimer's disease, Huntington's and Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, types of glaucoma, retina degeneration, especially retinitis pigmentosa, as well as general or diabetic peripheral neuropathy.

The invention relates primarily to the use of compounds of formula I, wherein
A signifies methylene, carbonyl or thiocarbonyl,
R represents amino, lower-alkylamino; phenyl-lower-alkylamino or phenyl-lower-alkyl-lower-alkylamino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-

lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, dilower-alkylamino-lower-alkinyl-lower-alkylamino; carboxy-lower-alkylamino, lower-alkoxycarbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, carboxy-lower-alkyl-lower-alkylamino, lower-alkoxycarbonyl-lower-alkyl-lower-alkylamino, carbamoyl-lower-alkyl-lower-alkylamino, cyano-lower-alkyl-lower-alkylamino, respectively 3- to 8-membered lower-alkyleneamino, lower-alkenyleneamino or lower-alkadienylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkylene-amino; or a benzyl-lower-alkyleneamino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

and their pharmaceutically employable salts, as well as compounds of formula I as such, and their salts, as well as processes for the production thereof.

The invention relates primarily for example to the use of compounds of formula I, wherein

A signifies methylene, carbonyl or thiocarbonyl,

R represents amino, lower-alkylamino; phenyl-lower-alkylamino or phenyl-lower-alkyl-lower-alkylamino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-

lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, dilower-alkylamino-lower-alkinyl-lower-alkylamino; carboxy-lower-alkylamino, lower-alkoxycarbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, carboxy-lower-alkyl-lower-alkylamino, lower-alkoxycarbonyl-lower-alkyl-lower-alkylamino, carbamoyl-lower-alkyl-lower-alkylamino, cyano-lower-alkyl-lower-alkylamino, 3- to 8-membered lower-alkyleneamino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkylene-amino and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

and their pharmaceutically employable salts, as well as compounds of formula I as such, and their salts, as well as processes for the production thereof.

The invention relates in particular to the use of compounds of formula I, wherein

A signifies methylene or carbonyl,

R represents C_1-C_4-alkylamino, such as methylamino, ethylamino, propylamino or butylamino; phenyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as benzylamino or phenethylamino, phenyl-C_1-C_4-alkyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number

up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as N-benzyl-N-methylamino; C_2-C_7-alkenylamino such as allylamino, methallylamino or but-2-enylamino, C_2-C_7-alkinylamino such as propargylamino or but-2-inylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino such as N-allyl-N-methylamino, N-allyl-N-ethylamino, N-methallyl-N-methylamino or N-but-2-enyl-N-methylamino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino such as N-propargyl-N-methylamino, N-propargyl-N-ethylamino or N-but-2-inyl-N-methylamino, di-C_1-C_4-alkylamino such as dimethylamino, diethylamino, N-methyl-N-propylamino or N-butyl-N-methylamino, carboxy-C_1-C_4-alkylamino, such as carboxymethylamino, lower-alkoxy-carbonyl-C_1-C_4-alkylamino, such as methoxy- or ethoxycarbonylaminomethyl, carbamoyl-C_1-C_4-alkylamino, such as carbamoylmethylamino, cyano-C_1-C_4-alkylamino, such as cyanomethylamino, N-carboxy-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, such as carboxymethyl-methylamino, N-lower-alkoxycarbonyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, such as methoxy- or ethoxycarbonylmethyl-methylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, such as carbamoylmethyl-methylamino, N-cyano-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, such as cyanomethyl-methylamino, pyrrolo (pyrrol-1-yl), pyrrolino (2,5-dihydropyrrol-1-yl), pyrrolidino, phenyl-C_1-C_4-alkylpyrrolidino, such as benzylpyrrolidino, piperidino, 1,2,3,6-tetrahydropyridino; phenyl-C_1-C_4-alkylpiperidino either unsubstituted or substituted by C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as benzyl-piperidino, morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, such as N'-methylpiperazino, N'-(hydroxy-C_2-C_4-alkyl)piperazino, such as N'-(2-hydroxyethyl)piperazino; or phenyl-C_1-C_4-alkylpiperazino either unsubstituted or substituted by C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as N'-benzylpiperazino, and
R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine or trifluoromethyl,
and their pharmaceutically employable salts, as well as new compounds of formula I defined as above, as such, and their salts, as well as processes for the production thereof.

The invention relates in particular for example to the use of compounds of formula I, wherein
A signifies methylene or carbonyl,

R represents C_1-C_4-alkylamino, such as methylamino, ethylamino, propylamino or butylamino; phenyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as benzylamino or phenethylamino, phenyl-C_1-C_4-alkyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as N-benzyl-N-methylamino; C_2-C_7-alkenylamino such as allylamino, methallylamino or but-2-enylamino, C_2-C_7-alkinylamino such as propargylamino or but-2-inylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino such as N-allyl-N-methylamino, N-allyl-N-ethylamino, N-methallyl-N-methylamino or N-but-2-enyl-N-methylamino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino such as N-propargyl-N-methylamino, N-propargyl-N-ethylamino or N-but-2-inyl-N-methylamino, di-C_1-C_4-alkylamino such as dimethylamino, diethylamino, N-methyl-N-propylamino or N-butyl-N-methylamino, carboxy-C_1-C_4-alkylamino, such as carboxymethylamino, lower-alkoxycarbonyl-C_1-C_4-alkylamino, such as methoxy- or ethoxycarbonylaminomethyl, carbamoyl-C_1-C_4-alkylamino, such as carbamoylmethylamino, cyano-C_1-C_4-alkylamino, such as cyanomethylamino, N-carboxy-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, such as N-carboxymethyl-N-methylamino, N-lower-alkoxycarbonyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, such as N-methoxy- or N-ethoxycarbonylmethyl-N-methylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, such as N-carbamoylmethyl-N-methylamino, cyano-C_1-C_4-alkyl-C_1-C_4-alkylamino, such as cyanomethyl-methylamino, pyrrolidino, piperidino, morpholino, piperazino, N'-C_1-C_4-alkyl-piperazino, such as N'-methylpiperazino or N'-(hydroxy-C_2-C_4-alkyl)piperazino, such as N'-(2-hydroxyethyl)piperazino, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine or trifluoromethyl,

and their pharmaceutically employable salts, as well as new compounds of formula I defined as above, as such, and their salts, as well as processes for the production thereof.

The invention preferably relates on the one hand to compounds of formula I, wherein

A signifies methylene or carbonyl,

R represents C_2-C_7-alkenylamino such as allylamino, methallylamino or but-2-enylamino, C_2-C_7-alkinylamino such as propargylamino or but-2-inylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino such as N-allyl-N-methylamino, N-allyl-N-ethylamino, N-methallyl-N-methylamino or

N-but-2-enyl-N-methylamino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino such as N-propargyl-N-methylamino, N-propargyl-N-ethylamino or N-but-2-inyl-N-methylamino; carbamoyl-C_1-C_4-alkylamino, such as carbamoylmethylamino, cyano-C_1-C_4-alkylamino, such as cyanomethylamino, carbamoyl-C_1-C_4-alkyl-C_1-C_4-alkylamino, such as carbamoylmethyl-methylamino, cyano-C_1-C_4-alkyl-C_1-C_4-alkylamino, such as cyanomethyl-methylamino; or phenyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine, and/or by trifluoromethyl; such as benzylamino or phenethylamino, and
R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine and/or trifluoromethyl,
and their salts, processes for their production and their use.

The invention preferably relates on the other hand to compounds of formula I, wherein
A signifies methylene or carbonyl,
R signifies pyrrolidino, pyrrolino (2,5-dihydropyrrol-1-yl), pyrrolo (pyrrol-1-yl), piperidino, tetrahydropyridino, such as 1,2,5,6-tetrahydropyridino or 1,2,3,4-tetrahydropyridino, morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, such as N'-methylpiperazino, or N'-(hydroxy-C_2-C_4-alkyl)piperazino, such as N'-(2-hydroxyethyl)piperazino, morpholino, thiomorpholino, S-oxothiomorpholino or S,S-dioxothiomorpholino, and
R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine and/or trifluoromethyl,
and their salts, processes for their production and their use.

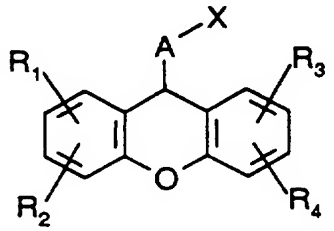
The invention relates primarily to compounds of formula I, wherein
A is methylene,
R represents C_2-C_7-alkenylamino such as allylamino, methallylamino or but-2-enylamino, C_2-C_7-alkinylamino such as propargylamino or but-2-inylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino such as N-allyl-N-methylamino, N-allyl-N-ethylamino, N-methallyl-N-methylamino or N-but-2-enyl-N-methylamino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino such as N-propargyl-N-methylamino, N-propargyl-N-ethylamino or N-but-2-inyl-N-methylamino, or cyano-C_1-C_4-alkyl-C_1-C_4-alkylamino, such as cyanomethyl-methylamino, and

R_1, R_2, R_3 and R_4 signify hydrogen, C_1-C_4-alkyl such as methyl, C_1-C_4-alkoxy such as methoxy, halogen with an atomic number up to and including 35 such as chlorine or bromine and/or trifluoromethyl,
and their salts, processes for their production and their use.

The invention most preferably relates to compounds of formula I, wherein
A is methylene,
R represents C_2-C_7-alkenylamino such as allylamino, methallylamino or but-2-enylamino, C_2-C_7-alkinylamino such as propargylamino or but-2-inylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkyl-amino such as N-allyl-N-methylamino, N-allyl-N-ethylamino, N-methallyl-N-methylamino or N-but-2-enyl-N-methylamino, or N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino such as N-propargyl-N-methylamino, N-propargyl-N-ethylamino or N-but-2-inyl-N-methylamino and
R_1 and R_3, independently of one another, signify hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen or trifluoromethyl and
R_2, R_4 signify hydrogen,
and their salts.

The invention relates particularly to the compounds of formula I named in the examples, and the pharmaceutically employable salts thereof, and their use.

The process for the production of new compounds of formula I is characterised in that a compound of formula II



(II),

wherein X signifies reactive, esterified hydroxy, or where A represents carbonyl or thiocarbonyl, it signifies free or etherified hydroxy, and R_1, R_2, R_3 and R_4 have the significances indicated,
is condensed with a compound of formula III

Y—R (III)

wherein Y signifies optionally intermediately protected amino, and R has the significance indicated,
and the optionally intermediately introduced amino protecting groups are cleaved,
and, if desired, a compound which is obtainable according to this process is converted into another compound of formula I, an isomeric mixture which is obtainable according to this process is separated into its components and the desired isomer isolated and/or a salt which is obtainable according to this process is converted into the free compound or a free compound which is obtainable according to this process is converted into a salt.

Reactive, esterified hydroxy in the starting materials of formula II is for example hydroxy which is esterified with a hydrohalic acid or an organic sulphonic acid, such as halogen, e.g. chlorine, bromine or iodine, benzene-sulphonyloxy optionally substituted by lower alkyl, halogen and/or nitro, such as benzene-sulphonyloxy, p-bromobenzene-sulphonyloxy or p-toluene-sulphonyloxy, or optionally halogenated lower-alkane-sulphonyloxy such as methane-sulphonyloxy or trifluoromethane-sulphonyloxy. Etherified hydroxy is for example lower alkoxy or a phenyl or phenyl-lower-alkyl group optionally substituted by lower alkyl, lower alkoxy, halogen and/or nitro.

The reaction of compounds of formulae II and III is effected in conventional manner, for example in the presence of a basic condensation agent, such as a tertiary or sterically hindered binary organic nitrogen base, such as a tri-lower-alkylamine or sterically hindered di-lower-alkylamine, such as triethylamine or diisopropylamine, or a hetero-aromatic base such as pyridine or dimethylaminopyridine, starting from compounds of formula II, wherein X is hydroxy, advantageously in the presence of a water-binding agent, such as a carbodiimide, for example N-dimethylaminopropyl-N'-ethyl-carbodiimide, preferably in an organic solvent such as a halogenated aliphatic hydrocarbon, e.g. dichloromethane, or toluene, and if necessary with cooling or heating, e.g. in a temperature range of ca. 0°C to ca. 80°C.

The amino protecting groups which may be considered are those which are usual for the intermediate protection of primary amino groups, especially solvolytically cleavable amino protecting groups. These are for example acyl groups derived from a carboxylic acid or a semi-ester of carbonic acid, such as optionally halogenated lower alkanoyl, for example

lower alkanoyl such as formyl, acetyl or pivaloyl, polyhalogen-lower-alkanoyl such as trifluoroacetyl, lower-alkoxycarbonyl such as methoxycarbonyl, ethoxycarbonyl, isopropyl-oxycarbonyl, or tertiary-butyloxycarbonyl, or optionally substituted phenyl-lower-alkoxy-carbonyl such as benzyloxycarbonyl, furthermore silyl groups such as tri-lower-alkylsilyl, e.g. trimethylsilyl.

Cleavage of these amino protecting groups is effected in conventional manner, for example by treatment with a solvolysis agent, such as with water in the presence of an acid, e.g. an aqueous mineral acid such as hydrohalic acid, or an alkali metal hydroxide such as caustic soda or caustic potash solution, especially for cleaving a tri-lower-alkoxycarbonyl, a sulphonic acid such as methanesulphonic acid in a halogenated hydrocarbon such as dichloromethane, or in particular for cleaving formyl, an appropriate silyl compound such as a tri-lower-alkylsilyl halide, such as trimethylsilyl bromide, or a disilazane such as hexamethyldisilazane.

The starting materials of formulae II and III are known or may be produced analogously to the method of forming known compounds of formulae II and III. Thus, compounds of formula II, wherein A is methylene and X is trifluoromethane-sulphonyloxy, are obtained for example by reacting the corresponding hydroxymethyl compound with trifluoromethanesulphonic acid anhydride in an ether, such as diethylether. The hydroxy-methyl compound to be used for this may be obtained by means of conventional reduction of the corresponding carboxylic acid or a lower alkylester therof, for example by means of a reaction with a di-light metal hydride, such as lithium aluminium hydride.

Compounds that are obtainable according to this process may be converted in conventional manner into other compounds of formula I.

In compounds of formula I, wherein R signifies unsubstituted amino and/or R_5 signifies hydrogen, the amino group may be substituted in conventional manner by one or two identical or different monovalent aliphatic or araliphatic radicals or one divalent aliphatic radical. Similarly, in compounds of formula I, wherein R signifies amino which is substituted by a monovalent aliphatic or araliphatic radical, a further monovalent aliphatic or araliphatic radical may also be introduced.

In compounds of formula I in particular, carbonyl or thiocarbonyl may be reduced to methylene in conventional manner, for example by means of reduction with a di-light metal hydride, such as lithium aluminium hydride in tetrahydrofuran.

The salts obtained may be converted in a manner known *per se* into the free compounds, e.g. by treatment with a base, such as an alkali metal hydroxide, a metal carbonate or hydrogen carbonate, or another salt-forming base mentioned initially, or with an acid such as a mineral acid, e.g. hydrochloric acid, or another salt-forming acid mentioned initially.

The salts obtained may be converted in a manner known *per se* into other salts, acid addition salts, e.g. by means of treatment with an appropriate metal salt, such as a sodium, barium or silver salt, or another acid in an appropriate solvent in which the inorganic salt being formed is insoluble and thus separates from the equilibrium of the reaction, and base salts, by releasing them from the free acid and forming the salt again.

The compounds of formula I, including their salts, may also be obtained in the form of hydrates, or may include the solvents used for crystallisation.

As a result of the close relationship between the new compounds in free form and in the form of their salts, in the preceding and following text, the free compounds and their salts are understood to also optionally refer to the corresponding salts and free compounds, as appropriate.

Owing to the physical-chemical differences in their constituents, the diastereoisomeric mixtures and racemic mixtures may be separated in known manner into the pure diastereoisomers and racemates, for example by means of chromatography and/or fractional crystallisation.
The racemates obtained may also be dissociated by known methods into the optical antipodes, for example by recrystallisation from an optically active solvent, with the assistance of micro-organisms or by reacting the diastereoisomeric mixture or racemate obtained with an optically active adjuvant compound, e.g. corresponding to the acidic, basic or functionally variable groups contained in compounds of formula I with an optically active acid, base or an optically active alcohol, into mixtures of diastereoisomeric salts or

functional derivatives such as esters, separating them into the diastereoisomers, from which the respectively desired enantiomers may be released in the usual manner. Bases, acids or alcohols that are suitable for this are for example optically active alkaloid bases, such as strychnine, cinchonine or brucine, or D- or L-(1-phenyl)ethylamine, 3-pipecoline, ephedrin, amphetamine and similar synthetically accessible bases, optically active carboxylic or sulphonic acids, such as quinic acid or D- or L-tartaric acid, D- or L-di-o-toluyl-tartaric acid, D- or L-malic acid, D- or L-mandelic acid, or D- or L-camphorsulphonic acid, or optically active alcohols, such as borneol or D- or L-(1-phenyl)ethanol.

The invention also relates to those embodiments of the process according to which it is possible to start from a compound obtainable as an intermediate product at any stage of the process and to carry out the missing steps, or to use a starting material in salt form or in particular to form the same under the reaction conditions.

As further preferred objects of the invention, the invention relates to pharmaceutical preparations, which contain the compounds of formula I according to the invention or pharmaceutically employable salts thereof as active ingredients, as well as processes for the production thereof.

The pharmaceutical preparations according to the invention, which contain the compound according to the invention or pharmaceutically employable salts thereof, are intended for enteral, such as oral, also rectal, and parenteral administration to warm-blooded animals, whereby the pharmacological active ingredient contained therein is on its own or together with a pharmaceutically employable carrier material. The daily dosage of the active ingredient depends on the age and individual condition as well as on the method of application.

The new pharmaceutical preparations contain e.g. from ca. 10% to ca. 80%, preferably from ca. 20% to ca. 60%, of the active ingredient. Pharmaceutical preparations according to the invention for enteral or parenteral administration are e.g. those in single dose form, such as dragées, tablets, capsules or suppositories, furthermore ampoules. These are produced in a manner known *per se*, e.g. by means of conventional mixing, granulating, dragée-forming, dissolving or lyophilisation processes. Thus, pharmaceutical preparations for oral application may be obtained by combining the active ingredient with solid carrier

substances, optionally granulating the mixture obtained, and processing the mixture or granulate into tablets or dragée cores, if desired or if necessary after adding appropriate excipients.

Appropriate carriers are in particular fillers such as sugar, e.g. lactose, saccharose, mannitol or sorbitol, cellulose preparations and/or calcium phosphates, e.g. tricalcium phosphate or calcium hydrogen phosphate, furthermore binding agents such as starch paste using e.g. corn, wheat, rice or potato starch, gelatin, tragacanth, methyl cellulose and/or polyvinyl-pyrrolidone, if desired, disintegrants such as the above-mentioned starches, furthermore carboxymethyl starch, crosslinked polyvinylpyrrolidone, agar, alginic acid or a salt thereof such as sodium alginate. Excipients are primarily mobile phases, mobile phase regulators and lubricants, e.g. silicic acid, talc, stearic acid or salts thereof such as magnesium or calcium stearate, and/or polyethylene glycol. Dragée cores are provided with appropriate coatings that are resistant to gastric juices if required. Those used include *inter alia* concentrated sugar solutions which optionally contain gum arabic, talc, polyvinyl pyrrolidone, polyethylene glycol and/or titanium dioxide, or lacquer solutions in appropriate organic solvents or solvent mixtures, or to produce coatings that are resistant to gastric juices, solutions of appropriate cellulose preparations such as acetyl cellulose phthalate or hydroxypropylmethyl cellulose phthalate. Dyes or pigments may be added to the tablets or dragée coatings, e.g. to identify or characterise different dosages of active ingredient.

Further orally applicable pharmaceutical preparations are hard two-piece gelatin capsules, as well as soft, closed capsules consisting of gelatin and a softener such as glycerol or sorbitol. The hard capsules may contain the active ingredient in the form of a granulate, e.g. mixed with fillers such as lactose, binding agents such as starches, and/or lubricants such as talc or magnesium stearate, and optionally stabilizers. In soft capsules, the active ingredient is preferably dissolved or suspended in appropriate liquids such as fatty oils, paraffin oil or liquid polyethylene glycols, whereby stabilizers may similarly be added.

Suppositories may be considered e.g. as rectally applicable pharmaceutical preparations. These consist of a combination of the active ingredient with a suppository base. Suitable suppository bases may be e.g. natural or synthetic triglycerides, paraffin hydrocarbons, polyethylene glycols or higher alkanols. In addition, rectal capsules of gelatin may also be

used, which contain a combination of the active ingredient with a base substance. The base substances may be e.g. liquid triglycerides, polyethylene glycols or paraffin hydrocarbons.

For parenteral administration by infusion and/or injection, aqueous solutions of an active ingredient in water-soluble form are primarily suitable, e.g. a water-soluble salt, also suspensions of the active ingredient, such as appropriate oily suspensions, whereby suitable lipophilic solvents or vehicles are used, such as fatty oils, sesame oil, or synthetic fatty acid esters, e.g. ethyl oleate or triglycerides, or aqueous suspensions which contain viscosity-increasing substances, e.g. sodium carboxymethyl cellulose, sorbitol and/or dextran, and optionally also stabilizers.

The dosage of active substance depends on the species of warm-blooded animal, the age and the individual condition, as well as the method of application. Under normal circumstances, for a patient of about 75 kg weight, an approximately daily dose for oral application is from ca. 10 mg to ca. 500 mg.

The following examples serve to illustrate the invention; temperatures are indicated in degrees celsius, and pressures in mbar.

Example 1: 1-(xanthen-9-ylmethyl)pyrrolidine

1.4 g (29.0 mmols) of lithium aluminium hydride are added in portions at 0°C to a solution of 5.41 g (19.3 mmols) of 1-(xanthene-9-carbonyl)pyrrolidine in 54 ml of tetrahydrofuran, and the suspension stirred at room temperature for 4 hours. The reaction mixture is hydrolysed with 1 N caustic soda solution and water, and filtered. The residue is taken up in ethyl acetate three times, heated under reflux for 30 minutes and filtered off. The organic phases are combined and concentrated. The solid is recrystallised from hexane. Following precipitation with hydrogen chloride from ether, the hydrochloride of 1-(xanthen-9-ylmethyl)pyrrolidine is obtained; M.p. 100-101°; ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.75 (m, 4H); 2.50 (m, 4H); 2.68 (d, 2H); 4.05 (t, 1H); 7.0-7.35 (m, 8H); FAB-MS: 266 (M+), 195, 181.

Example 2: 1-(xanthene-9-carbonyl)morpholine

A solution of 1.2 g (5.3 mmols) of xanthene-9-carboxylic acid, 1.25 g (6.5 mmols) of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide-hydrochloride, 0.798 g (6.5 mmols) of 4-

dimethylaminopyridine, 0.57 ml (6.5 mmols) of morpholine and 50 ml of dichloromethane is stirred for 20 hours at room temperature under argon, subsequently concentrated and chromatographed on silica gel (hexane/ethyl acetate 95:5). Xanthene-9-carboxylic acid-morpholinyl-amide is obtained as a crystalline product; M.p. 177-178°; ^{1}H-NMR ($CDCl_3$, 300 MHz): 3.16 (d, br, 4H); 3.62 (s, br, 4H); 5.45 (s, 1H); 7.02-7.31 (m, 8H).

Example 3: 1-(xanthen-9-ylmethyl)morpholine

A suspension of 0.7 g (2.37 mmols) of 1-(xanthene-9-carbonyl)morpholine in 50 ml of ether is added in drops at 15-20° to 0.4 g (10.5 mmols) of lithium aluminium hydride in 20 ml of ether, and stirred at room temperature for 1.5 hours. The reaction mixture is mixed with ammonium sulphate solution whilst cooling with ice, taken up in ethyl acetate, and washed with water and saturated sodium chloride solution. The organic phases are dried with sodium sulphate and concentrated on a rotary evaporator. The residue is chromatographed on silica gel (hexane/ethyl acetate 97.5:2.5) and 1-(xanthen-9-ylmethyl)morpholine is yielded as a crystalline compound; M.p. 98-99°; ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.42 (dd, 4H); 2.55 (d, 2H); 3.66 (dd, 4H); 4.03 (t, 1H); 7.0-7.35 (m, 8H).

Example 4: xanthene-9-carboxylic acid propargylamide

A solution of 2.4 g (10.6 mmols) of xanthene-9-carboxylic acid, 2.5 g (13 mmols) of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide-hydrochloride, 1.6 g (13 mmols) of 4-dimethyl-aminopyridine, 0.833 ml (13 mmols) of propargylamine and 100 ml of dichloromethane is stirred for 20 hours at room temperature under argon, subsequently concentrated and chromatographed on silica gel (hexane/ethyl acetate 7:3). Xanthene-9-carboxylic acid propargylamide is isolated as a crystalline product; M.p. 238-239°; ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.12 (dd, 1H); 3.92 (dd, 2H); 4.92 (s, 1H); 5.44 (s,br, 1H); 7.10-7.45 (m, 8H).

Example 5: N-(xanthen-9-ylmethyl)-propargylamine

A solution of 1.06 g (5 mmols) of 9-hydroxymethyl-xanthene, 3.49 ml (25 mmols) of triethyl-amine and 10 ml of dichloromethane is added in drops, under argon, at -75°C, to a solution of 2.2 ml (13.5 mmols) of trifluoromethane-sulphonic acid anhydride in 50 ml of dichloromethane, and stirred for 15 minutes at this temperature. 1.92 ml (30 mmols) of propargylamine are subsequently added in drops and the solution is heated to room temperature over 2 hours. The reaction is stirred for a further 4 hours at room temperature,

then mixed with ethyl acetate, and the organic phase is washed with saturated sodium chloride solution, saturated sodium chloride solution, dried with sodium sulphate and concentrated on a rotary evaporator. Following chromatography on silica gel (hexane/ethyl acetate 95:5), N-(9-xanthylmethyl)-propargylamine is obtained; ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.19 (s, 1H); 2.92 (d, 2H); 3.37 (s, 2H); 4.14 (t, 1H); 7.05-7.35 (m, 8H).

Example 6: N-methyl-xanthene-9-carboxylic acid-propargylamide

A solution of 1.2 g (5.3 mmols) of xanthene-9-carboxylic acid, 1.25 g (6.5 mmols) of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide-hydrochloride, 0.798 g (6.5 mmols) of 4-dimethylaminopyridine, 0.55 ml (6.5 mmols) of N-methylpropargylamine and 50 ml of dichloromethane is stirred for 20 hours at room temperature under argon, subsequently taken up in ethyl acetate, and the organic phases are washed with saturated $NaHCO_3$ solution, water and saturated sodium chloride solution, dried with sodium sulphate and concentrated on a rotary evaporator. The crude product is chromatographed on silica gel (hexane/ethyl acetate 95:5). N-methyl-xanthene-9-carboxylic acid-propargylamide is obtained as a crystalline product;

M.p. 116-117°; ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.20 (s, br, 1H); 2.80 (s, br, 3H); 4.23 (s, 2H); 5.49 (s, 1H); 7.01-7.31 (m, 8H).

Example 7: N-methyl-N-(xanthen-9-ylmethyl)-propargylamine

0.7 g (2.53 mmols) of N-methyl-xanthene-9-carboxylic acid-propargylamide in 50 ml of ether are added in drops at 0°C to a suspension of 0.4 g (10.53 mmols) of lithium aluminium hydride in 20 ml of ether, and stirred for 1 hour. The reaction is slowly hydrolysed with diluted ammonium suphate solution, the suspension taken up in ethyl acetate, the organic phases are washed with saturated sodium chloride solution, dried with sodium sulphate, and concentrated on a rotary evaporator. N-methyl-N-(9-xanthylmethyl)-propargylamine is obtained by chromatography on silica gel and crystallisation from methanol;

M.p. 63-63°; ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.19 (s, 1H); 2.34 (s, 3H); 2.66 (d, 2H); 3.33 (s, 2H); 4.00 (t, 1H); 7.05-7.35 (m, 8H).

Example 8: N-methyl-xanthene-9-carboxylic acid-cyanomethylamide

A solution of 2.4 g (10.6 mmols) of xanthene-9-carboxylic acid, 2.5 g (13 mmols) of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide-hydrochloride, 3.18 g (26 mmols) of 4-dimethyl-

-aminopyridine, 1.38 g (13 mmols) of N-methylaminoacetonitrile-hydrochloride and 100 ml of dichloromethane is stirred for 20 hours at room temperature under argon, subsequently concentrated and chromatographed on silica gel (hexane/ethyl acetate 9:1). N-methyl-xanthene-9-carboxylic acid-cyanomethylamide is isolated as a crystalline product;
M.p. 166-167°; ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.81 (s, 3H); 4.30 (s, 2H); 5.52 (s, 1H); 7.05-7.35 (m, 8H).

Example 9: N-methyl-N-(xanthen-9-ylmethyl)-cyanomethylamine
A solution of 1.06 g (5 mmols) of 9-hydroxymethyl-xanthene, 2.1 ml (15 mmols) of triethyl-amine and 10 ml of ether is added in drops at -70°C, under argon, to a solution of 2.46 ml (15 mmols) of trifluorosulphonic acid anhydride in 50 ml of ether, and stirred for 15 minutes at this temperature. Subsequently, 3.5 g (50 mmols) of N-methylaminoacetonitrile are added in drops, and the solution heated to room temperature over 1.5 hours. The reaction is stirred for a further hour at room temperature, and then 3.5 g (50 mmols) of N-methyl-aminoacetonitrile are added twice, with a one hour interval, and the reaction is stirred for a further 16 hours, then mixed with ethyl acetate, and the organic phase is washed with saturated sodium chloride solution, saturated sodium chloride solution, dried with sodium sulphate and concentrated on a rotary evaporator. Chromatography on silica gel (hexane/ethyl acetate 98:2) produces N-methyl-N-(9-xanthylmethyl)-cyanomethylamine, which is recrystallised from ether/hexane;
M.p. 112.113°; ^{1}H-NMR ($CDCl_3$, 300 MHz): 2.38 (s, 3H); 2.71 (d, 2H); 3.44 (s, 2H); .4.02 (t, 1H); 7.05-7.30 (m, 8H).

Example 10: 1-(xanthen-9-ylmethyl)pyrrolidinium hydrogen maleate
1.90 g (16.4 mmols) of maleic acid in 45 ml of methanol are added at room temperature to a solution of 4.34 g (16.4 mmols) of 1-(xanthen-9-ylmethyl)pyrrolidine (example 1) in 20 ml of methylene chloride and 25 ml of methanol. Afterwards, the product is concentrated on a rotary evaporator to a total volume of 30 ml, and left to crystallise over night. 1.07 g (17%) of title compound, hydrogen maleinate of 1-(xanthen-9-ylmethyl)pyrrolidine, are obtained as white crystal needles; M.p. 168-169°; ^{1}H-NMR (CD_3OD, 200 MHz): 1.98 (m, 4H); 3.30 (m br, 4H); 3.50 (d, 2H); 4.61 (t, 1H); 6.25 (s, 2H, maleic acid); 7.15-7.48 (m, 8H); ES-MS: 266 (M+), 195.
Analysis: C: 69.17 (69.28); H: 6.04 (6.08); N: 3.67 (3.67).

Example 11: 1-(xanthen-9-ylmethyl)pyrrolidinium hydrogen fumarate

2.37 g (20.5 mmols) of fumaric acid in 15 ml of methanol are added at room temperature to a solution of 5.43 g (20.5 mmols) of 1-(xanthen-9-ylmethyl)pyrrolidine (example 1) in 20 ml of methylene chloride and 25 ml of methanol. Afterwards, the product is concentrated on a rotary evaporator to a total volume of 30 ml, and left to crystallise over night. 4.12 g (53%) of title compound, hydrogen fumarate of 1-(xanthen-9-ylmethyl)pyrrolidine, are obtained as white needles; M.p. 174-176°;

^{1}H-NMR (CD_3OD, 200 MHz): 1.97 (m, 4H); 3.20 (m, 4H); 3.43 (d, 2H); 4.61 (t, 1H); 6.78 (s, 2H, fumaric acid); 7.15-7.49 (m, 8H); ES-MS: 266 (M+), 195;

Analysis: C: 69.32 (69.28); H: 6.12 (6.08); N: 3.62 (3.67).

Example 12: 1-(xanthene-9-thiocarbonyl)pyrrolidine

A solution of 1.5 g (5.4 mmols) of 1-(9-xanthylcarbonyl)-pyrrolidine in 20 ml of THF is mixed with 2.17 g (5.4 mmols) of Lawson's reagent and stirred over night at room temperature. The product is concentrated and chromatographed on silica gel with hexane/ethyl acetate (= 9:1) as eluant. 1.12 g (71%) of xanthene-9-carboxylic acid pyrrolidyl-thioamide are obtained as a white powder; M.p. 180-190°; ^{1}H-NMR ($CDCl_3$, 200 MHz): 1.75 (m, 4H); 3.05 (t, 2H); 3.85 (t, 2H); 6.24 (s, 1H); 7.00-7.45 (m, 8H).;^{13}C-NMR ($CDCl_3$, 50 MHz): 24.01; 27.22; 50.67; 54.78; 56.32; 117.15; 119.03; 124.08; 128.77; 129.56; 150.52; 198.55 (C=S); ES-MS: 296 (M+).

Example 13: 1-(xanthene-9-carbonyl)-1,2,5,6-tetrahydro-pyridine

A solution of 1.2 g (5.3 mmols) of xanthene-9-carboxylic acid, 1.25 g (6.5 mmols) of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide-hydrochloride, 0.79 g (6.5 mmols) of DMAP, 0.54 g (6.5 mmols) of 1,2,3,6-tetrahydropyridine and 50 ml of CH_2Cl_2 is stirred for 17 hours at room temperature under argon, subsequently concentrated, and chromatographed on silica gel with hexane/ethyl acetate (9:1) as eluant. The title compound is isolated as a crystalline product;

M.p. 116-117°; ^{1}H-NMR ($CDCl_3$, 300 MHz): 1.5 (m, 2H); 2.15 (m, 1H); 3.27 (t, 2H); 3.73 (m, 2H); 4.08 (s, 2H); 5.47 (s, 1H); 5.52 (m, br, 1H); 5.62 (s, 1H); 7.00-7.30 (m, 8H).

Example 14: 1-(xanthen-9-ylmethyl)-1,2,5,6-tetrahydro-pyridine-hydrochloride

0.7 g (2.53 mmols) of 1-(xanthene-9-carbonyl)-1,2,5,6-tetrahydro-pyridine in 50 ml of ether is slowly added in drops at 0°C to a suspension of 0.4 g (10.53 mmols) of $LiAlH_4$ in 20 ml of ether, and stirred for 6 hours. The reaction is slowly hydrolysed with 3 ml of methanol, the suspension taken up in ethyl acetate, the organic phases washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated on a rotary evaporator. Following chromatography on silica gel, with a subsequent reaction to the hydrochloride by passing in hydrochloric acid in a THF solution, 1-(xanthen-9-ylmethyl)-1,2,5,6-tetrahydro-pyridine-hydrochloride is obtained as a foam; Thin-layer chromatography (silica gel, ethyl acetate/hexane 1:1) of the free base: Rf= 0.63; ^{1}H-NMR ($CDCl_3$, 300 Mhz): 2.11 (m, 2H); 2.52 (t, 2H); 2.58 (d, 2H); 2.96 (m, 2H); 4.08 (t, 1H); 5.62 (m, 1H); 5.75 (m, 1H); 7.00-7.35 (m, 8H).

Example 15: 1-(xanthene-9-carbonyl)-2,5-dihydro-pyrrole

A solution of 1.2 g (5.3 mmols) of xanthene-9-carboxylic acid, 1.25 g (6.5 mmols) of N-(3-dimethylaminopropyl)-N'-ethyl-carbodiimide-hydrochloride, 0.79 g (6.5 mmols) of DMAP, 0.36 g (5.2 mmols) of 65% 2,5-dihydropyrroline/35% pyrrolidine and 30 ml of CH_2Cl_2 is stirred for 18 hours at room temperature under argon, subsequently taken up in ethyl acetate, the organic phases are washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated on a rotary evaporator, and chromatographed on silica gel with hexane/ethyl acetate (7:3) as eluant. The title compound is isolated as a crystalline product;

M.p. 162-163°; ^{1}H-NMR ($CDCl_3$, 300 Mhz): 3.80 (m, 2H); 4.28 (m, 2H); 5.40 (s, 1H); 5.56 (m, 1H); 5.74 (m, 1H); 7.00-7.32 (m, 8H).

Example 16: 1-(xanthen-9-ylmethyl)-2,5-dihydro-pyrrole and 1-(xanthen-9-ylmethyl)-pyrrole

0.6 g (2.53 mmols) of 1-(xanthen-9-ylcarbonyl)-2,5-dihydro-pyrrole in 50 ml of ether/THF (1:1) are slowly added in drops at 0°C to a suspension of 0.45 g (11.9 mmols) of $LiAlH_4$ in 20 ml of ether, and stirred for 3 hours at room temperature. The reaction is slowly hydrolysed at 0°C with 2 ml of methanol, the suspension is taken up in ethyl acetate/hexane, the organic phases are washed with saturated sodium chloride solution, dried over sodium sulphate and concentrated on a rotary evaporator. Following chromatography on silica gel (ethyl acetate/hexane 15:85), 1-(xanthylene-9-methyl)-2,5-

dihydro-pyrrole is obtained as a crystalline product; M.p. 87-90°; ^{1}H-NMR ($CDCl_3$, 300 Mhz): 2.90 (d, 2H); 3.50 (s, br, 4H); 4.01 (1, 1H); 5.72 (s, 2H); 7.00-7.35 (m, 8H).

During the reduction of 1-(xanthen-9-ylcarbonyl)-2,5-dihydro-pyrrole with $LiAlH_4$, 1-(xanthen-9-ylmethyl)pyrrole is obtained as a by-product, and is isolated by chromatography on silica gel with ethyl acetate/hexane (9:1) as eluant; M.p. 86-88°; ^{1}H-NMR ($CDCl_3$, 300 Mhz): 4.03 (d, 2H); 4.29 (t, 1H); 6.08 (dd, 2H); 6.31 (dd, 2H); 6.85-7.32 (m, 8H).

Example 17: Tablets, each containing 50 mg of N-(xanthen-9-ylmethyl)-propargylamine, may be produced as follows:

Composition (10,000 tablets)

active ingredient	500.0 g
lactose	500.0 g
potato starch	352.0 g
gelatin	8.0 g
talc	60.0 g
magnesium stearate	10.0 g
siicon dioxide (highly disperse)	20.0 g
ethanol	q.s.

The active ingredient is mixed with the lactose and 292 g of potato starch, the mixture moistened with an ethanolic solution of the gelatin and granulated through a sieve. After drying, the remainder of the potato starch, the magnesium stearate, the talc and the silicon dioxide are mixed in, and the mixture is pressed into tablets each of 145.0 mg weight and 50.0 mg active ingredient content. If desired, they may be provided with partial notches for finer adjustment of the dosage.

Example 18: A sterile-filtered aqueous gelatin solution with 20% cyclodextrins as dissolving intermediary, each containing 3 mg of N-(xanthen-9-ylmethyl)-propargylamine as active ingredient, is mixed whilst heating, under aseptic conditions, with a sterile gelatin solution containing phenol as a preservative, such that 1.0 ml of solution has the following composition:

active ingredient	3 mg
gelatin	150.0 mg
phenol	4.7 mg
dist. water with 20% cyclodextrins as dissolving intermediary	1.0 ml

Example 19: To produce a sterile dry substance for injection, each containing 5 mg of N-(9-xanthylmethyl)-propargylamine, 5 mg of one of the compounds of formula I named in the preceding examples as the active ingredient are dissolved in 1 ml of an aqueous solution with 20 mg of mannitol and 20% cyclodextrins as dissolving intermediary. The solution is sterile-filtered and filled into a 2 ml ampoule under aseptic conditions, deep-frozen and lyophilized. Prior to usage, the lyophilzate is dissolved in 1 ml of distilled water or 1 ml of physiological sodium chloride solution. The solution is used intramuscularly or intravenously. This formulation may also be filled into double-chamber injection ampoules.

Example 20: For the production of 10,000 lacquer-coated tablets, each containing 100 mg of
N-(xanthen-9-ylmethyl)-propargylamine, the following procedure may be followed:

active ingredient	1000 g
corn starch	680 g
colloidal silicic acid	200 g
magnesium stearate	20 g
stearic acid	50 g
sodium carboxymethyl starch	250 g
water	q.s.

A mixture of one of the compounds of formula I named in the preceding examples as active ingredient, 50 g of corn starch and the colloidal silicic acid is worked into a moist mass with starch paste consisting of 250 g of corn starch and 2.2 kg of demineralised water. This mass is forced through a sieve of 3 mm mesh size, and dried for 30 minutes at 45° in a fluidised bed drier. The dried granulate is pressed through a sieve of 1 mm mesh size, mixed with a previously-sieved mixture (1 mm sieve) of 330 g of corn starch, the

magnesium stearate, the stearic acid and the sodium carboxymethyl starch, and then pressed into slightly domed tablets.

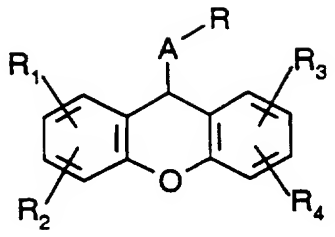
Example 21: In addition, pharmaceutical preparations containing another compound according to one of examples 1 to 16 or

xanthene-9-carboxylic acid amide;
1-(xanthene-9-carbonyl)-4-methyl-piperazine;
1-(xanthene-9-methyl)-4-methyl-piperazine;
1-(xanthene-9-carbonyl)pyrrolidine alias xanthene-9-carboxylic acid pyrrolidide;
1-(xanthene-9-carbonyl)piperidine alias xanthene-9-carboxylic acid piperidide;
xanthene-9-carboxylic acid-N-methyl-N-(2-diethylaminoethyl)-amide;
1-(xanthen-9-ylmethyl)piperidine or
1-(xanthen-9-ylmethyl)-N-methyl-N-(2-diethylaminoethyl)-amine

or a pharmaceutically employable salt thereof, may be produced analogously to the methods described in examples 17 to 20.

Patent Claims:

1. A compound of formula I



(I),

wherein A signifies methylene, carbonyl or thiocarbonyl,
R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic or araliphatic radicals, and
R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl, with the provision that

a) at least one of radicals R_1, R_2, R_3 and R_4 is different from hydrogen, if R signifies amino, chloroacetylamino, 2-diethylaminoethylamino or piperidino, or if R represents lower-alkylamino, di-lower-alkylamino, pyrrolidino, morpholino or 4-lower-alkyl-piperazino and A represents carbonyl;

b) R_1 and R_3 are different from hydrogen, lower alkyl and halogen or R is different from optionally 4-lower-alkylated 4-amino- or 4-hydroxypiperidino, if R_2 and R_4 signify hydrogen and A is methylene;

c) R_1 is different from 2-methoxy, R_2 from 3-methoxy, R_3 from 7-methoxy or R_4 from 6-methoxy, if R is methylamino or acetylamino and A is methylene;

d) R_1 is different from 2-ethoxycarbonyl, R_3 from 7-chloro, if R is 4-methylpiperazino, R_2 and R_4 signify hydrogen and A represents methylene,

and their salts.

2. A compound according to claim 1, wherein
A signifies methylene, carbonyl or thiocarbonyl,
R represents amino, lower-alkylamino; phenyl-lower-alkylamino or phenyl-lower-alkyl-lower-alkylamino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino,

lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, dilower-alkylamino-lower-alkinyl-lower-alkylamino; carboxy-lower-alkylamino, lower-alkoxycarbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, carboxy-lower-alkyl-lower-alkylamino, lower-alkoxycarbonyl-lower-alkyl-lower-alkylamino, carbamoyl-lower-alkyl-lower-alkylamino, cyano-lower-alkyl-lower-alkylamino, respectively 3- to 8-membered lower-alkyleneamino, lower-alkenyleneamino or lower-alkadienylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkylene-amino; or a benzyl-lower-alkyleneamino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

and their salts.

3. A compound according to claim 1, wherein

A signifies methylene, carbonyl or thiocarbonyl,

R represents amino, lower-alkylamino; phenyl-lower-alkylamino or phenyl-lower-alkyl-lower-alkylamino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino,

lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkyl-amino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkyl-amino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, dilower-alkylamino-lower-alkinyl-lower-alkylamino; carboxy-lower-alkylamino, lower-alkoxycarbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, carboxy-lower-alkyl-lower-alkylamino, lower-alkoxycarbonyl-lower-alkyl-lower-alkylamino, carbamoyl-lower-alkyl-lower-alkylamino, cyano-lower-alkyl-lower-alkylamino, 3- to 8-membered lower-alkyleneamino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkylene-amino and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

and their salts.

4. A compound according to claim 1, wherein

A signifies methylene or carbonyl,

R represents C_1-C_4-alkylamino; phenyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; phenyl-C_1-C_4-alkyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including and/or trifluoromethyl; C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkyl-amino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, carboxy-C_1-C_4-alkylamino, lower-alkoxycarbonyl-C_1-C_4-alkylamino, carbamoyl-C_1-C_4-alkylamino, cyano-C_1-C_4-alkyl-amino, N-carboxy-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-lower-alkoxycarbonyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-cyano-C_1-C_4-alkyl-N-C_1-

C_4-alkylamino, pyrrolo, pyrrolino, pyrrolidino, phenyl-C_1-C_4-alkylpyrrolidino, piperidino, 1,2,3,6-tetrahydropyridino; phenyl-C_1-C_4-alkylpiperidino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, N'-(hydroxy-C_2-C_4-alkyl)piperazino; or phenyl-C_1-C_4-alkylpiperazino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 or trifluoromethyl,

and their salts.

5. A compound according to claim 1, wherein

A signifies methylene or carbonyl,

R represents C_1-C_4-alkylamino; phenyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; phenyl-C_1-C_4-alkyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, carboxy-C_1-C_4-alkylamino, lower-alkoxycarbonyl-C_1-C_4-alkylamino, carbamoyl-C_1-C_4-alkylamino, cyano-C_1-C_4-alkylamino, N-carboxy-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-lower-alkoxycarbonyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-cyano-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, pyrrolo, pyrrolino, pyrrolidino, piperidino, morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, or N'-(hydroxy-C_2-C_4-alkyl)piperazino, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 or trifluoromethyl,

and their salts.

6. A compound according to claim 1, wherein

A is methylene,

R represents C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino or N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, carbamoyl-C_1-C_4-alkylamino, cyano-C_1-C_4-alkylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino or cyano-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl, and their salts.

7. A compound according to claim 1, wherein
A signifies methylene or carbonyl,
R signifies pyrrolidino, pyrrolino, pyrrolo, piperidino, tetrahydropyridino, morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, N'-(hydroxy-C_2-C_4-alkyl)piperazino, morpholino, thiomorpholino, S-oxothiomorpholino or S,S-dioxothiomorpholino, and
R_1, R_2, R_3 and R_4, independently of one another, signify hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl, and their salts.

8. A compound according to claim 1, wherein
A is methylene,
R represents C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, or cyano-C_1-C_4-alkyl-C_1-C_4-alkylamino, and
R_1 and R_3, independently of one another, signify hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen or trifluoromethyl, and R_2, R_4 signify hydrogen,
and their salts.

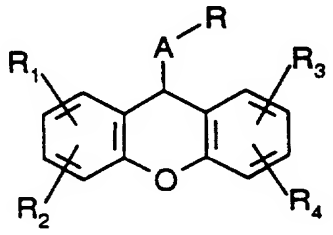
9. A compound according to claim 1, selected from
1-(xanthen-9-ylmethyl)pyrrolidine;
1-(xanthene-9-carbonyl)morpholine;
1-(xanthen-9-ylmethyl)morpholine;
xanthene-9-carboxylic acid propargylamide;
N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthene-9-carboxylic acid propargylamide;
N-methyl-N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthen-9-carboxylic acid cyanomethylamide;
N-methyl-N-(xanthen-9-ylmethyl)-cyanomethylamine;
1-(xanthene-9-thiocarbonyl)pyrrolidine;
1-(xanthene-9-carbonyl)-1,2,5,6-tetrahydro-pyridine;

1-(9-xanthylmethyl)-1,2,5,6-tetrahydro-pyridine;
1-(xanthene-9-carbonyl)-2,5-dihydro-pyrrole;
1-(xanthen-9-ylmethyl)-2,5-dihydro-pyrrole and
1-(xanthen-9-ylmethyl)pyrrole
and their pharmaceutically employable salts.

10. A compound according to one of claims 1 to 9 in free form or in a pharmaceutically employable salt form, for application in a process for the therapeutic treatment of humans or animals.

11. Pharmaceutical preparation, containing a compound according to one of claims 1 to 10, or a pharmaceutically employable salt thereof, together with the usual pharmaceutical excipients and carriers.

12. Process for the production of compounds of formula I



(I),

wherein A signifies methylene, carbonyl or thiocarbonyl,
R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic or araliphatic radicals, and
R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl, with the provision that

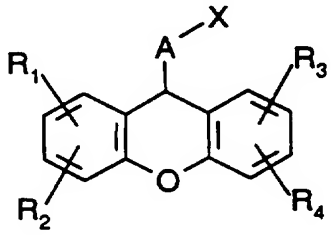
a) at least one of radicals R_1, R_2, R_3 and R_4 is different from hydrogen, if R signifies amino, chloroacetylamino, 2-diethylaminoethylamino or piperidino, or if R represents lower-alkylamino, di-lower-alkylamino, pyrrolidino, morpholino or 4-lower-alkyl-piperazino and A represents carbonyl;

b) R_1 and R_3 are different from hydrogen, lower alkyl and halogen or R is different from optionally 4-lower-alkylated 4-amino- or 4-hydroxypiperidino, if R_2 and R_4 signify hydrogen and A is methylene;

c) R_1 is different from 2-methoxy, R_2 from 3-methoxy, R_3 from 7-methoxy or R_4 from 6-methoxy, if R is methylamino or acetylamino and A is methylene;

d) R_1 is different from 2-ethoxycarbonyl, R_3 from 7-chloro, if R is 4-methylpiperazino, R_2 and R_4 signify hydrogen and A represents methylene,

and their salts, characterised in that a compound of formula II



(II),

wherein X signifies reactive, esterified hydroxy, or where A represents carbonyl or thiocarbonyl, it signifies free or etherified hydroxy, and R_1, R_2, R_3 and R_4 have the significances indicated,

is condensed with a compound of formula III

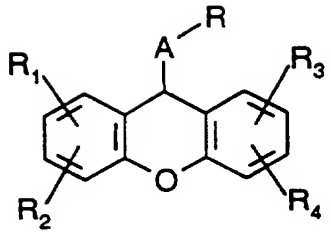
$$Y—R \qquad (III)$$

wherein Y signifies optionally intermediately protected amino, and R has the significance indicated,

and the optionally intermediately introduced amino protecting groups are cleaved,

and, if desired, a compound which is obtainable according to this process is converted into another compound of formula I, an isomeric mixture which is obtainable according to this process is separated into its components and the desired isomer isolated and/or a salt which is obtainable according to this process is converted into the free compound or a free compound which is obtainable according to this process is converted into a salt.

13. Use of a compound of formula I



(I),

wherein A signifies methylene, carbonyl or thiocarbonyl,

R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic or araliphatic radicals, in free form or in the form of a pharmaceutically employable salt, as an anti-neurodegenerative medicament, or for the production thereof.

14. Use of a compound of formula I according to claim 13, wherein

A signifies methylene, carbonyl or thiocarbonyl,

R represents amino, lower-alkylamino; phenyl-lower-alkylamino or phenyl-lower-alkyl-lower-alkylamino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, dilower-alkylamino-lower-alkinyl-lower-alkylamino; carboxy-lower-alkylamino, lower-alkoxycarbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, carboxy-lower-alkyl-lower-alkylamino, lower-alkoxycarbonyl-lower-alkyl-lower-alkylamino, carbamoyl-lower-alkyl-lower-alkylamino, cyano-

lower-alkyl-lower-alkylamino, respectively 3- to 8-membered lower-alkyleneamino, lower-alkenyleneamino or lower-alkadienylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkylene-amino; or a benzyl-lower-alkyleneamino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

in free form or in the form of a pharmaceutically employable salt, as an anti-neurodegenerative medicament, or for the production thereof.

15. Use of a compound of formula I according to claim 13, wherein

A signifies methylene or carbonyl,

R represents C_1-C_4-alkylamino; phenyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; phenyl-C_1-C_4-alkyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkyl-amino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, carboxy-C_1-C_4-alkylamino, lower-alkoxycarbonyl-C_1-C_4-alkylamino, carbamoyl-C_1-C_4-alkylamino, cyano-C_1-C_4-alkyl-amino, N-carboxy-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-lower-alkoxycarbonyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-cyano-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, pyrrolo, pyrrolino, pyrrolidino, phenyl-C_1-C_4-alkylpyrrolidino, piperidino, 1,2,3,6-tetrahydropyridino; phenyl-C_1-C_4-alkylpiperidino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, N'-(hydroxy-C_2-C_4-alkyl)piperazino; or phenyl-C_1-C_4-alkylpiperazino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 or trifluoromethyl,

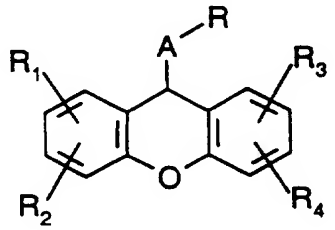
in free form or in the form of a pharmaceutically employable salt, as an anti-neurodegenerative medicament, or for the production thereof.

16. Use of a compound of formula I according to claim 13, wherein
A signifies methylene or carbonyl,
R represents C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino or N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, carbamoyl-C_1-C_4-alkylamino, cyano-C_1-C_4-alkylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, cyano-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, pyrrolidino, pyrrolino, pyrrolo, piperidino, tetrahydropyridino, morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, N'-(hydroxy-C_2-C_4-alkyl)piperazino, morpholino, thiomorpholino, S-oxothiomorpholino or S,S-dioxothiomorpholino, and
R_1, R_2, R_3 and R_4, independently of one another, signify hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl,
in free form or in the form of a pharmaceutically employable salt, as an anti-neurodegenerative medicament, or for the production thereof.

17. Use of a compound of formula I according to claim 13, selected from
1-(xanthen-9-ylmethyl)pyrrolidine;
1-(xanthene-9-carbonyl)morpholine;
1-(xanthen-9-ylmethyl)morpholine;
xanthene-9-carboxylic acid propargylamide;
N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthene-9-carboxylic acid propargylamide;
N-methyl-N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthen-9-carboxylic acid cyanomethylamide;
N-methyl-N-(xanthen-9-ylmethyl)-cyanomethylamine;
1-(xanthene-9-thiocarbonyl)pyrrolidine;
1-(xanthene-9-carbonyl)-1,2,5,6-tetrahydro-pyridine;
1-(xanthen-9-ylmethyl)-1,2,5,6-tetrahydro-pyridine;
1-(xanthene-9-carbonyl)-2,5-dihydro-pyrrole;
1-(xanthen-9-ylmethyl)-2,5-dihydro-pyrrole and
1-(xanthen-9-ylmethyl)pyrrole
xanthene-9-carboxylic acid amide;
1-(xanthene-9-carbonyl)-4-methyl-piperazine;
1-(xanthen-9-ylmethyl)-4-methyl-piperazine;

1-(xanthene-9-carbonyl)-pyrrolidine;
1-(xanthene-9-carbonyl)-piperidine;
1-(xanthen-9-ylmethyl)-piperidine;
xanthene-9-carboxylic acid-N-methyl-N-(2-diethylaminoethyl)-amide and
N-(xanthene-9-methyl)-N-methyl-N-(2-diethylaminoethyl)-amine
in free form or in the form of a pharmaceutically employable salt, as an anti-neurodegenerative medicament, or for the production thereof.

18. Process for the treatment of neurodegenerative disorders, especially those in which apoptotic cytolysis plays a role, such as cerebral ischaemia, Alzheimer's disease, Huntington's and Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, types of glaucoma, retina degeneration, especially retinitis pigmentosa, as well as general or diabetic peripheral neuropathia, characterised in that a therapeutically effective quantity of a compound of formula I



(I),

wherein A signifies methylene, carbonyl or thiocarbonyl,
R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic or araliphatic radicals, in free form or in the form of a pharmaceutically employable salt,
is administered to a warm-blooded person or animal requiring such treatment.

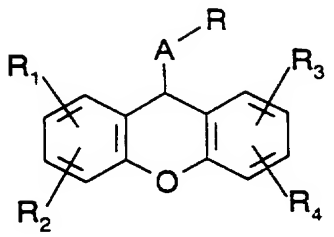
19. Treatment process according to claim 18, characterised in that a therapeutically effective quantity of a compound selected from
1-(xanthen-9-ylmethyl)pyrrolidine;
1-(xanthene-9-carbonyl)morpholine;
1-(xanthen-9-ylmethyl)morpholine;
xanthene-9-carboxylic acid propargylamide;
N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthene-9-carboxylic acid propargylamide;

N-methyl-N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthen-9-carboxylic acid cyanomethylamide;
N-methyl-N-(xanthen-9-ylmethyl)-cyanomethylamine;
1-(xanthene-9-thiocarbonyl)pyrrolidine;
1-(xanthene-9-carbonyl)-1,2,5,6-tetrahydro-pyridine;
1-(xanthen-9-ylmethyl)-1,2,5,6-tetrahydro-pyridine;
1-(xanthene-9-carbonyl)-2,5-dihydro-pyrrole;
1-(xanthen-9-ylmethyl)-2,5-dihydro-pyrrole and
1-(xanthen-9-ylmethyl)pyrrole
xanthene-9-carboxylic acid amide;
1-(xanthene-9-carbonyl)-4-methyl-piperazine;
1-(xanthen-9-ylmethyl)-4-methyl-piperazine;
1-(xanthene-9-carbonyl)-pyrrolidine;
1-(xanthene-9-carbonyl)-piperidine;
xanthene-9-carboxylic acid-N-methyl-N-(2-diethylaminoethyl)-amide and
N-(xanthene-9-methyl)-N-methyl-N-(2-diethylaminoethyl)-amine
is administered in free form or in the form of a pharmaceutically employable salt.

AMENDED CLAIMS

[received by the International Bureau on 25 November 1997 (25.11.97);
original claims 1, 9 and 12 amended;
remaining claims unchanged (13 pages)]

1. A compound of formula I



(I),

wherein A signifies methylene, carbonyl or thiocarbonyl,

R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic or araliphatic radicals, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl, with the provision that

a) at least one of radicals R_1, R_2, R_3 and R_4 is different from hydrogen, if A is thiocarbonyl and R is amino, chloracetylamino, 2-diethylaminoethylamino or piperidino;

b) at least one of radicals R_1, R_2, R_3 and R_4 is different from hydrogen, if A is methylene and R is amino, chloracetylamino, 2-diethylaminoethylamino, piperidino, 4-(lower-alkyl)piperazino, N-[β-di(lower-alkyl)aminoethyl]-N-methylamino, 4-hydroxy-4-t-butyl-piperidino, β-piperidino-methyl, β-pyrrolidino-methyl, β-(di-lower-alkyl-amino) methyl or 2,6-bis(1-methylethyl)phenyl-aminocarbonylamino;

c) at least one of radicals R_1, R_2, R_3 and R_4 is different from hydrogen, if A is carboxy and R is amino, chloracetylamino, di(lower-alkyl)amino-lower-alkyl-amino, piperidino, lower-alkylamino, di-lower-alkylamino, pyrrolidino, morpholino, 4-lower-alkyl-piperazino, pyrrolidinoethylamino, 4-(β-carboxyethyl)phenethylamino, 4-(β-ethoxycarbonylethyl)phenethylamino, 4-carboxyphenethylamino, 4-ethoxycarbonyl-phenethylamino, N-(β-diethylaminoethyl)-N-phenylamino, N-benzyl-N-(β-diethylaminoethyl)amino, N-β-morpholinoethyl-N-benzylamino, N-δ-piperidinobutyl-N-[β-(3,4-dimethylphenyl)ethyl]amino, N-δ-dimethylaminobutyl-N-(3-methylcyclopentyl)amino, N-(β-diethylaminoethyl)-N-(2-methyl-1,2,3,6-

tetrahydrobenzyl)amino, morpholino-lower-alkyl-amino or piperidino-lower-alkyl-amino;

d) R_1 and R_3 are different from hydrogen, lower alkyl and halogen or R is different from optionally 4-lower-alkylated 4-amino- or 4-hydroxypiperidino, if R_2 and R_4 signify hydrogen and A is methylene;

e) R_1 is different from 2-methoxy, R_2 from 3-methoxy, R_3 from 7-methoxy or R_4 from 6-methoxy, if R is methylamino or acetylamino and A is methylene;

f) R_1 is different from 2-ethoxycarbonyl, R_3 from 7-chloro, if R is 4-methylpiperazino, R_2 and R_4 signify hydrogen and A represents methylene,

and their salts.

2. A compound according to claim 1, wherein

A signifies methylene, carbonyl or thiocarbonyl,

R represents amino, lower-alkylamino; phenyl-lower-alkylamino or phenyl-lower-alkyl-lower-alkylamino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkyl-amino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkyl-amino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, dilower-alkylamino-lower-alkinyl-lower-alkylamino; carboxy-lower-alkylamino, lower-alkoxycarbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, carboxy-lower-alkyl-lower-alkylamino, lower-alkoxycarbonyl-lower-alkyl-lower-alkylamino, carbamoyl-lower-alkyl-lower-alkylamino, cyano-lower-alkyl-lower-alkylamino, respectively 3- to 8-membered lower-alkyleneamino, lower-

alkenyleneamino or lower-alkadienylene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkylene-amino; or a benzyl-lower-alkyleneamino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

and their salts.

3. A compound according to claim 1, wherein

A signifies methylene, carbonyl or thiocarbonyl,

R represents amino, lower-alkylamino; phenyl-lower-alkylamino or phenyl-lower-alkyl-lower-alkylamino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkyl-amino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkyl-amino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, dilower-alkylamino-lower-alkinyl-lower-alkylamino; carboxy-lower-alkylamino, lower-alkoxycarbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, carboxy-lower-alkyl-lower-alkylamino, lower-alkoxycarbonyl-lower-alkyl-lower-alkylamino, carbamoyl-lower-alkyl-lower-alkylamino, cyano-lower-alkyl-lower-alkylamino, 3- to 8-membered lower-alkyleneamino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl,

lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkylene-amino and
R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,
and their salts.

4. A compound according to claim 1, wherein
A signifies methylene or carbonyl,
R represents C_1-C_4-alkylamino; phenyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; phenyl-C_1-C_4-alkyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including and/or trifluoromethyl; C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkyl-amino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, carboxy-C_1-C_4-alkylamino, lower-alkoxycarbonyl-C_1-C_4-alkylamino, carbamoyl-C_1-C_4-alkylamino, cyano-C_1-C_4-alkyl-amino, N-carboxy-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-lower-alkoxycarbonyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-cyano-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, pyrrolo, pyrrolino, pyrrolidino, phenyl-C_1-C_4-alkylpyrrolidino, piperidino, 1,2,3,6-tetrahydropyridino; phenyl-C_1-C_4-alkylpiperidino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, N'-(hydroxy-C_2-C_4-alkyl)piperazino; or phenyl-C_1-C_4-alkylpiperazino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl, and
R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 or trifluoromethyl,
and their salts.

5. A compound according to claim 1, wherein
A signifies methylene or carbonyl,
R represents C_1-C_4-alkylamino; phenyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; phenyl-C_1-C_4-alkyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or

trifluoromethyl; C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, carboxy-C_1-C_4-alkylamino, lower-alkoxycarbonyl-C_1-C_4-alkylamino, carbamoyl-C_1-C_4-alkylamino, cyano-C_1-C_4-alkylamino, N-carboxy-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-lower-alkoxycarbonyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-cyano-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, pyrrolo, pyrrolino, pyrrolidino, piperidino, morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, or N'-(hydroxy-C_2-C_4-alkyl)piperazino, and
R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 or trifluoromethyl,
and their salts.

6. A compound according to claim 1, wherein
A is methylene,
R represents C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino or N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, carbamoyl-C_1-C_4-alkylamino, cyano-C_1-C_4-alkylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino or cyano-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, and
R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl,
and their salts.

7. A compound according to claim 1, wherein
A signifies methylene or carbonyl,
R signifies pyrrolidino, pyrrolino, pyrrolo, piperidino, tetrahydropyridino, morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, N'-(hydroxy-C_2-C_4-alkyl)piperazino, morpholino, thiomorpholino, S-oxothiomorpholino or S,S-dioxothiomorpholino, and
R_1, R_2, R_3 and R_4, independently of one another, signify hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl,
and their salts.

8. A compound according to claim 1, wherein
A is methylene,
R represents C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, or cyano-C_1-C_4-alkyl-C_1-C_4-alkylamino, and

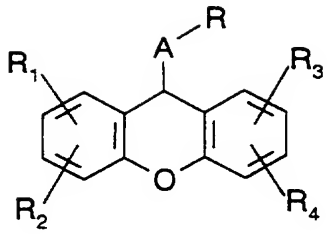
R_1 and R_3, independently of one another, signify hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen or trifluoromethyl, and R_2, R_4 signify hydrogen,
and their salts.

9. A compound selected from
1-(xanthen-9-ylmethyl)pyrrolidine;
1-(xanthene-9-carbonyl)morpholine;
1-(xanthen-9-ylmethyl)morpholine;
xanthene-9-carboxylic acid propargylamide;
N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthene-9-carboxylic acid propargylamide;
N-methyl-N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthen-9-carboxylic acid cyanomethylamide;
N-methyl-N-(xanthen-9-ylmethyl)-cyanomethylamine;
1-(xanthene-9-thiocarbonyl)pyrrolidine;
1-(xanthene-9-carbonyl)-1,2,5,6-tetrahydro-pyridine;
1-(9-xanthylmethyl)-1,2,5,6-tetrahydro-pyridine;
1-(xanthene-9-carbonyl)-2,5-dihydro-pyrrole;
1-(xanthen-9-ylmethyl)-2,5-dihydro-pyrrole and
1-(xanthen-9-ylmethyl)pyrrole
and their pharmaceutically employable salts.

10. A compound according to one of claims 1 to 9 in free form or in a pharmaceutically employable salt form, for application in a process for the therapeutic treatment of humans or animals.

11. Pharmaceutical preparation, containing a compound according to one of claims 1 to 10, or a pharmaceutically employable salt thereof, together with the usual pharmaceutical excipients and carriers.

12. Process for the production of compounds of formula I



(I),

wherein A signifies methylene, carbonyl or thiocarbonyl,

R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic or araliphatic radicals, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl, with the provision that

a) at least one of radicals R_1, R_2, R_3 and R_4 is different from hydrogen, if A is thiocarbonyl and R is amino, chloracetylamino, 2-diethylaminoethylamino or piperidino;

b) at least one of radicals R_1, R_2, R_3 and R_4 is different from hydrogen, if A is methylene and R is amino, chloracetylamino, 2-diethylaminoethylamino, piperidino, 4-(lower-alkyl)piperazino, N-[β-di(lower-alkyl)aminoethyl]-N-methylamino, 4-hydroxy-4-t-butyl-piperidino, β-piperidino-methyl, β-pyrrolidino-methyl, β-(di-lower-alkyl-amino) methyl or 2,6-bis(1-methylethyl)phenyl-aminocarbonylamino;

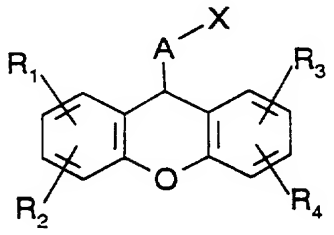
c) at least one of radicals R_1, R_2, R_3 and R_4 is different from hydrogen, if A is carboxy and R is amino, chloracetylamino, di(lower-alkyl)amino-lower-alkyl-amino, piperidino, lower-alkylamino, di-lower-alkylamino, pyrrolidino, morpholino, 4-lower-alkyl-piperazino, pyrrolidinoethylamino, 4-(β-carboxyethyl)phenethylamino, 4-(β-ethoxycarbonylethyl)phenethylamino, 4-carboxyphenethylamino, 4-ethoxycarbonyl-phenethylamino, N-(β-diethylaminoethyl)-N-phenylamino, N-benzyl-N-(β-diethylaminoethyl)amino, N-β-morpholinoethyl-N-benzylamino, N-δ-piperidinobutyl-N-[β-(3,4-dimethylphenyl)ethyl]amino, N-δ-dimethylaminobutyl-N-(3-methylcyclopentyl)amino, N-(β-diethylaminoethyl)-N-(2-methyl-1,2,3,6-tetrahydrobenzyl)amino, morpholino-lower-alkyl-amino or piperidino-lower-alkyl-amino;

d) R_1 and R_3 are different from hydrogen, lower alkyl and halogen or R is different from optionally 4-lower-alkylated 4-amino- or 4-hydroxypiperidino, if R_2 and R_4 signify hydrogen and A is methylene;

e) R_1 is different from 2-methoxy, R_2 from 3-methoxy, R_3 from 7-methoxy or R_4 from 6-methoxy, if R is methylamino or acetylamino and A is methylene;

f) R_1 is different from 2-ethoxycarbonyl, R_3 from 7-chloro, if R is 4-methylpiperazino, R_2 and R_4 signify hydrogen and A represents methylene,

and their salts, characterised in that a compound of formula II



(II),

wherein X signifies reactive, esterified hydroxy, or where A represents carbonyl or thiocarbonyl, it signifies free or etherified hydroxy, and R_1, R_2, R_3 and R_4 have the significances indicated,

is condensed with a compound of formula III

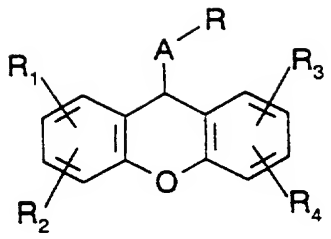
Y—R (III)

wherein Y signifies optionally intermediately protected amino, and R has the significance indicated,

and the optionally intermediately introduced amino protecting groups are cleaved,

and, if desired, a compound which is obtainable according to this process is converted into another compound of formula I, an isomeric mixture which is obtainable according to this process is separated into its components and the desired isomer isolated and/or a salt which is obtainable according to this process is converted into the free compound or a free compound which is obtainable according to this process is converted into a salt.

13. Use of a compound of formula I



(I),

wherein A signifies methylene, carbonyl or thiocarbonyl,
R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic or araliphatic radicals, in free form or in the form of a pharmaceutically employable salt, as an anti-neurodegenerative medicament, or for the production thereof.

14. Use of a compound of formuia I according to claim 13, wherein
A signifies methylene, carbonyl or thiocarbonyl,
R represents amino, lower-alkylamino; phenyl-lower-alkylamino or phenyl-lower-alkyl-lower-alkylamino either unsubstituted or substituted by lower alkyl, lower alkoxy, halogen and/or trifluoromethyl; hydroxy-lower-alkylamino, lower-alkoxy-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, lower-alkyleneamino-lower-alkylamino, lower-alkenylamino, hydroxy-lower-alkenylamino, lower-alkoxy-lower-alkenylamino, lower-alkanoyloxy-lower-alkenylamino, di-lower-alkylamino-lower-alkenylamino, lower-alkinylamino, hydroxy-lower-alkinylamino, lower-alkoxy-lower-alkinylamino, lower-alkanoyloxy-lower-alkinylamino, di-lower-alkylamino-lower-alkinylamino, di-lower-alkylamino, di(hydroxy-lower-alkyl)amino, hydroxy-lower-alkyl-lower-alkylamino, di(lower-alkoxy-lower-alkyl)amino, lower-alkoxy-lower-alkyl-lower-alkylamino, lower-alkanoyloxy-lower-alkylamino, lower-alkanoyloxy-lower-alkyl-lower-alkylamino, di-lower-alkylamino-lower-alkylamino, di-lower-alkylamino-lower-alkyl-lower-alkylamino, di-lower-alkenylamino, lower-alkenyl-lower-alkylamino, hydroxy-lower-alkenyl-lower-alkylamino, di(lower-alkoxy-lower-alkenyl)amino, lower-alkoxy-lower-alkenyl-lower-alkylamino, lower-alkanoyloxy-lower-alkenyl-lower-alkylamino, di-lower-alkylamino-lower-alkenyl-lower-alkylamino, lower-alkinyl-lower-alkylamino, lower-alkoxy-lower-alkinyl-lower-alkylamino, lower-alkanoyloxy-lower-alkinyl-lower-alkylamino, dilower-alkylamino-lower-alkinyl-lower-alkylamino; carboxy-lower-alkylamino, lower-alkoxycarbonyl-lower-alkylamino, carbamoyl-lower-alkylamino, cyano-lower-alkylamino, carboxy-lower-alkyl-lower-alkylamino, lower-alkoxycarbonyl-lower-alkyl-lower-alkylamino, carbamoyl-lower-alkyl-lower-alkylamino, cyano-

lower-alkyl-lower-alkylamino, respectively 3- to 8-membered lower-alkyleneamino, lower-alkenyleneamino or lower-alkadienyiene-amino; 3- or 4-aza-lower-alkylene-amino either unsubstituted or N-substituted by lower-alkyl, hydroxy-lower-alkyl, lower-alkoxy-lower-alkyl or lower-alkanoyl; 3- or 4-oxa-lower-alkylene-amino or optionally S-oxidised 3- or 4-thia-lower-alkylene-amino; or a benzyl-lower-alkyleneamino or N'-benzylaza-lower-alkylene-amino radical either unsubstituted or substituted in the phenyl moiety by lower aikyl, lower alkoxy, halogen and/or trifluoromethyl, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, lower alkyl, lower alkoxy, halogen or trifluoromethyl,

in free form or in the form of a pharmaceutically employable salt, as an anti-neurodegenerative medicament, or for the production thereof.

15. Use of a compound of formula I according to claim 13, wherein

A signifies methylene or carbonyl,

R represents C_1-C_4-alkylamino; phenyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; phenyl-C_1-C_4-alkyl-C_1-C_4-alkylamino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkyl-amino, N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, di-C_1-C_4-alkylamino, carboxy-C_1-C_4-alkylamino, lower-alkoxycarbonyl-C_1-C_4-alkylamino, carbamoyl-C_1-C_4-alkylamino, cyano-C_1-C_4-alkyl-amino, N-carboxy-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-lower-alkoxycarbonyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, N-cyano-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, pyrrolo, pyrrolino, pyrrolidino, phenyl-C_1-C_4-alkylpyrrolidino, piperidino, 1,2,3,6-tetrahydropyridino; phenyl-C_1-C_4-alkylpiperidino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl; morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, N'-(hydroxy-C_2-C_4-alkyl)piperazino; or phenyl-C_1-C_4-alkylpiperazino either unsubstituted or substituted by C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and inciuding 35 and/or trifluoromethyl, and

R_1, R_2, R_3 and R_4, independently of one another, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 or trifluoromethyl,

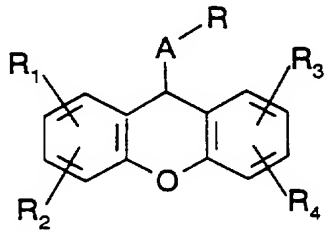
in free form or in the form of a pharmaceutically employable salt, as an anti-neurodegenerative medicament, or for the production thereof.

16. Use of a compound of formula I according to claim 13, wherein
A signifies methylene or carbonyl,
R represents C_2-C_7-alkenylamino, C_2-C_7-alkinylamino, N-C_2-C_7-alkenyl-N-C_1-C_4-alkylamino or N-C_2-C_7-alkinyl-N-C_1-C_4-alkylamino, carbamoyl-C_1-C_4-alkylamino, cyano-C_1-C_4-alkylamino, N-carbamoyl-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, cyano-C_1-C_4-alkyl-N-C_1-C_4-alkylamino, pyrrolidino, pyrrolino, pyrrolo, piperidino, tetrahydropyridino, morpholino, piperazino, N'-C_1-C_4-alkylpiperazino, N'-(hydroxy-C_2-C_4-alkyl)piperazino, morpholino, thiomorpholino, S-oxothiomorpholino or S,S-dioxothiomorpholino, and
R_1, R_2, R_3 and R_4, independently of one another, signify hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen with an atomic number up to and including 35 and/or trifluoromethyl,
in free form or in the form of a pharmaceutically employable salt, as an anti-neurodegenerative medicament, or for the production thereof.

17. Use of a compound of formula I according to claim 13, selected from
1-(xanthen-9-ylmethyl)pyrrolidine;
1-(xanthene-9-carbonyl)morpholine;
1-(xanthen-9-ylmethyl)morpholine;
xanthene-9-carboxylic acid propargylamide;
N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthene-9-carboxylic acid propargylamide;
N-methyl-N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthen-9-carboxylic acid cyanomethylamide;
N-methyl-N-(xanthen-9-ylmethyl)-cyanomethylamine;
1-(xanthene-9-thiocarbonyl)pyrrolidine;
1-(xanthene-9-carbonyl)-1,2,5,6-tetrahydro-pyridine;
1-(xanthen-9-ylmethyl)-1,2,5,6-tetrahydro-pyridine;
1-(xanthene-9-carbonyl)-2,5-dihydro-pyrrole;
1-(xanthen-9-ylmethyl)-2,5-dihydro-pyrrole and
1-(xanthen-9-ylmethyl)pyrrole
xanthene-9-carboxylic acid amide;
1-(xanthene-9-carbonyl)-4-methyl-piperazine;
1-(xanthen-9-ylmethyl)-4-methyl-piperazine;

1-(xanthene-9-carbonyl)-pyrrolidine;
1-(xanthene-9-carbonyl)-piperidine;
1-(xanthen-9-ylmethyl)-piperidine;
xanthene-9-carboxylic acid-N-methyl-N-(2-diethylaminoethyl)-amide and
N-(xanthene-9-methyl)-N-methyl-N-(2-diethylaminoethyl)-amine
in free form or in the form of a pharmaceutically employable salt, as an anti-neurodegenerative medicament, or for the production thereof.

18. Process for the treatment of neurodegenerative disorders, especially those in which apoptotic cytolysis plays a role, such as cerebral ischaemia, Alzheimer's disease, Huntington's and Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, types of glaucoma, retina degeneration, especially retinitis pigmentosa, as well as general or diabetic peripheral neuropathia, characterised in that a therapeutically effective quantity of a compound of formula I



(I),

wherein A signifies methylene, carbonyl or thiocarbonyl,
R represents an amino group, either unsubstituted or mono- or di-substituted by monovalent aliphatic and/or araliphatic radicals, or disubstituted by divalent aliphatic or araliphatic radicals, in free form or in the form of a pharmaceutically employable salt,
is administered to a warm-blooded person or animal requiring such treatment.

19. Treatment process according to claim 18, characterised in that a therapeutically effective quantity of a compound selected from
1-(xanthen-9-ylmethyl)pyrrolidine;
1-(xanthene-9-carbonyl)morpholine;
1-(xanthen-9-ylmethyl)morpholine;
xanthene-9-carboxylic acid propargylamide;
N-(xanthen-9-ylmethyl)-propargylamine;
N-methyl-xanthene-9-carboxylic acid propargylamide;

N-methyl-N-(xanthen-9-ylmethyl)-propargylamine;

N-methyl-xanthen-9-carboxylic acid cyanomethylamide;

N-methyl-N-(xanthen-9-ylmethyl)-cyanomethylamine;

1-(xanthene-9-thiocarbonyl)pyrrolidine;

1-(xanthene-9-carbonyl)-1,2,5,6-tetrahydro-pyridine;

1-(xanthen-9-ylmethyl)-1,2,5,6-tetrahydro-pyridine;

1-(xanthene-9-carbonyl)-2,5-dihydro-pyrrole;

1-(xanthen-9-ylmethyl)-2,5-dihydro-pyrrole and

1-(xanthen-9-ylmethyl)pyrrole

xanthene-9-carboxylic acid amide;

1-(xanthene-9-carbonyl)-4-methyl-piperazine;

1-(xanthen-9-ylmethyl)-4-methyl-piperazine;

1-(xanthene-9-carbonyl)-pyrrolidine;

1-(xanthene-9-carbonyl)-piperidine;

xanthene-9-carboxylic acid-N-methyl-N-(2-diethylaminoethyl)-amide and

N-(xanthene-9-methyl)-N-methyl-N-(2-diethylaminoethyl)-amine

is administered in free form or in the form of a pharmaceutically employable salt.

INTERNATIONAL SEARCH REPORT

Intern. .nal Application No
PCT/EP 97/02885

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D311/84 C07D311/90 C07D405/06 A61K31/35

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 26 32 200 A (PIERRE FABRE S.A.) 20 October 1977 see claims; example 2 ---	1-19
X	US 4 136 197 A (M. HÜBNER ET AL.) 23 January 1979 see claims; example 1 ---	1-19
X	US 2 676 971 A (J.W. CUSIC ET AL.) 27 April 1954 see the whole document ---	1-19
X	US 2 956 060 A (J. ROSICKY) 11 October 1960 see the whole document ---	1-19
	-/--	

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 1997	26.09.97

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Chouly, J

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INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/EP 97/02885

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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1

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/02885

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim(s) 13-19
is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter .nal Application No
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